REMARKS/ARGUMENTS

Reconsideration of this application is requested. Claims 1, 3, 4 and 10-17 are in the case. Claims 4 and 11-17 are withdrawn. Claims 1, 3 and 10 are under examination.

I. THE INTERVIEW

At the outset, the undersigned wishes to thank the Examiner (Mr. Rawlings) for kindly agreeing to conduct an interview on this case. The interview was held on April 26, 2010, and the time spent by the Examiner on the case was most appreciated.

As indicated in the Interview Summary, agreement was reached at the interview that if Applicant were to amend the claims to recite the language suggested in the outstanding Action, except for deletion of the word "selective", the outstanding formal matters would be obviated and the only remaining issue would be the obviousness rejection.

In light of the agreement reached at the interview, the claims have been amended as suggested in the Action, with the additional amendment to specify "in subjects who have been subjected to androgen ablation therapy". Basis for this amendment can be found at throughout the specification as filed and, in particular, in Example 1. No new matter is entered.

It is understood that the amendments presented herein are made without prejudice to pursuing broader subject matter in a continuing case, and to expedite prosecution. The presentation of the amendments is not to be taken as a concession to

the rejections. Withdrawal of the issues relating to priority and the formal rejections under 35 U.S.C. §112, first and second paragraphs, is respectfully requested.

II. THE OBVIOUSNESS REJECTIONS

Claims 1, 3 and 10 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Graff *et al.*, Clin. Cancer Res. 2001 Dec; **7**: 3857-3861 (Graff) in view of Church *et al. (J. Biol. Chem.* 2001 Aug 31; **276 (35):** 33156-33164) (Church), Attiga *et al.* (Cancer Res. 2000 Aug 15; 60: 46-29-4637) (Attiga), Liu *et al. (J. Urol.* 2000 Sep; 164: 820-825) (Liu), or Kelavkar *et al. (Carcinogenesis.* 2001 Nov; **22** (11): 1765-1773) (Kelavkar). The rejections are respectfully traversed.

As claimed, there is provided a method of inhibiting or reducing the proliferation of prostate cancer cells that express a $sPLA_2$-IIA polypeptide comprising the amino acid sequence of SEQ ID NO: 3 in a human subject who has been subjected to androgen ablation therapy. The method comprises administering to the subject a selective inhibitor of the enzyme activity of the polypeptide, wherein the inhibitor inhibits the ability of the polypeptide to catalyse the hydrolysis of membrane phospholipids at the sn-2 position to release fatty acids and lysophospholipids, wherein the inhibitor inhibits the $sPLA_2$-IIA-mediated proliferation of prostate cancer cells, and wherein the inhibitor is a cyclic peptide of the following formula:

A1-A2-A3-A4-A5, in which

A1 is F or Y or W or 2Nap

A2 is L or I

A3 is S or T

A4 is F or Y or W or 2Nap, and

A5 is R or K.

The Action asserts that Graff discloses that "enhanced sPLA2-IIA expression may be involved in the malignant progression of human prostate cancer and suggests that specific inhibitors of the group IIA sPLA2 may be useful for prostate cancer chemotherapy." The Action thus alleges that it would have been obvious to a person skilled in the art to have inhibited the growth or proliferation of prostate cancer cells by contacting the cells with an agent that inhibits the expression and/or activity of human sPLA2-IIA in prostate cancer cells, and would have been motivated to do so to treat prostate cancer. The Action asserts that one skilled in the art would have found it obvious to have inhibited the growth or proliferation of prostate cancer cells using the cyclic peptides described by Church and would have been motivated to do so to treat prostate cancer. The Action further asserts that one skilled in the art would have had a reasonable expectation of success in doing so in light of the disclosure by Attiga, Liu or Kelavkar. Attiga allegedly discloses that invasion of prostate cancer cells (i.e. PC-3 and DU-145 cells) is inhibited by a PLA2 inhibitor, a general COX inhibitor and a selected COX-2 inhibitor. Liu relates to a COX-2 inhibitor, and Kelavkar relates to a 15-lipooxygenase inhibitor.

In response, the disclosures of the cited art and certain conclusions arising therefrom are discussed in the attached executed Rule 132 declaration of Dr. Kieran Scott (a coinventor in the present case) (the declaration). At the outset, the declaration stresses the importance of the present invention in that it provides, for the first time, a

method of inhibiting the sPLA2-IIA-mediated proliferation of prostate cancer cells in late stage prostate cancer.

The declaration notes that Graff is cited as disclosing that "enhanced sPLA2-IIA expression may be involved in the malignant progression of human prostate cancer and suggests that specific inhibitors of the group hA sPLA2 may be useful for prostate cancer chemotherapy." The declaration notes that Church is cited as disclosing cyclic peptide inhibitors of sPLA2-IIA, and that Attiga is cited as disclosing that invasion of prostate cancer cells (i.e., PC-3 and DU-145 cells) is inhibited by a PLA2 inhibitor, a general COX inhibitor and a selected COX-2 inhibitor. The declaration observes that Liu is cited as disclosing a COX-2 inhibitor, and that Kelavkar is cited as disclosing a *15*-lipoxygenase inhibitor.

The declaration states that none of the documents referred to in the Action suggest to now or as of the filing date of the case (June, 2002) that inhibiting sPLA2-IIA-mediated proliferation of prostate cancer cells would produce a successful treatment for late stage prostate cancer. The declaration states that the cited documents are at best a collection of papers describing inhibitors of unrelated enzymes, with a paper describing that sPLA2-IIA expression is elevated in malignant progression and progression to androgen-independence, and a paper describing cyclic peptide inhibitors of sPLA2-IIA thrown into the mix. The declaration further observes that if it had been suggested to Dr. Scott before the present invention that inhibiting the sPLA2-IIA-mediated proliferation of prostate cancer cells after androgen ablation therapy would produce a successful treatment for late stage prostate cancer, Dr. Scott would have been skeptical based on his knowledge at the time of the role of sPLA2-IIA in prostate

cancer. The declaration provides an overview of progression of prostate cancer with reference to a Figure 1 which is a schematic diagram of the main events in the overall progression of prostate cancer. The discussion notes that it is well known in the art that malignant progression of prostate cancer cells (i.e., early stage prostate cancer) is both biochemically and functionally distinct from late stage (terminal) prostate cancer.

The declaration goes on to compare the present invention compared with Graff. The declaration observes that the present invention is directed towards (i) the inhibition of proliferation of prostate cancer cells and (ii) in cells of subjects who have been subjected to androgen ablation therapy (see Example 1 of the patent application). In other words, the declaration observes that the present case relates to the inhibition of the proliferation of prostate cancer cells following androgen ablation therapy after progression to androgen-independence has occurred (i.e., treatment of late stage prostate cancer).

Dr. Scott states that there is nothing in Graff that suggests that inhibition of sPLA2-IIA enzyme activity would produce a successful treatment for late stage prostate cancer, i.e., following androgen ablation therapy and after progression to androgen-independence has occurred (referring to Figure 1 in the declaration). Dr. Scott notes that Graff is clearly directed towards malignant progression of prostate cancer, i.e., early stage prostate cancer, as outlined in Figure 1 of the declaration (referring to the Conclusions, page 3857; Results and Discussion page 3859; and last paragraph of Results and Discussion on page 3860 of Graff). The declaration asserts that there is nothing in Graff to suggest that the inhibitors would be useful after progression to malignancy and androgen independence has occurred. At that stage, the present

application shows it becomes necessary to target a different biochemical mechanism such as cell proliferation. There is no evidence in Graff, according to the declaration, to suggest that inhibitors of sPLA2-IIA would be effective at inhibiting proliferation of prostate cancer cells that have already progressed to malignancy and androgen independence.

The declaration notes that malignant progression and progression to androgen-independence (as discussed in Graff) are both biochemically and functionally separable from the process of cellular proliferation as claimed. For example, the declaration states that aberrant cell proliferation, though necessary, is not sufficient for malignant progression. The declaration also notes that tumor growth is the result of a balance between the rate of cell proliferation and the rate of programmed cell death (apoptosis). Dr. Scott observes that tumor growth can be increased not only by increasing the rate of cell proliferation (as the present inventors have shown for sPLA2-IIA), but by changes that reduce the rate of apoptosis.

On this point, the declaration observes that reference 29, cited in the last paragraph of Graff (Denmeade *et al.,* 1996; Exhibit 3 hereto) shows that a major determinant of increased tumor growth in prostate cancer may not be increased rate of proliferation but enhanced cell survival due to suppression of cell death mechanisms (apoptosis). This prior art, cited in the last paragraph of Graff therefore would have suggested to the skilled person, according to Dr. Scott, to try a known inhibitor of apoptosis as a treatment for prostate cancer.

The declaration goes on to observe that the last paragraph of Graff states: "This report therefore provides compelling evidence that enhanced sPLA2-IIA expression may

be involved in malignant progression of human prostate cancer and suggests that specific inhibitors of the group hA sPLA2 may be useful for prostate cancer chemotherapy."

This conclusion is based, according to Dr. Scott, on findings that: (i) "the expression of Group hA sPLA2 is specifically increased with progression of human prostate cancer cells to androgen independence"; (ii) "sPLA2-IIA expression is dramatically increased in primary, high-grade prostate cancers"; (iii) "this increase is related to the increased proliferative index that typifies the more advanced CaPs (26, 29)"; and (iv) "sPLA2-IIA expression is inversely related to 5-year patient survival".

The declaration states that finding (i) by Graff is based on observations that the sPLA2-IIA expression levels are increased in androgen independent variants relative to their androgen-dependent parent cells. The androgen independent variants have been derived by selection either for androgen independent growth in culture or have been selected for androgen-independent growth of androgen-dependent tumours in immune-deficient mice (following castration). While the cell lines examined in Graff satisfy the criteria for progression to androgen independence in culture, it is important to note, according to Dr. Scott, that they have not been directly derived from patients who have been subjected to hormone ablation therapy, but have been derived from androgen-dependent prostate cells by *ex vivo* manipulation. Dr. Scott observes that the cell lines therefore do not directly derive from hormone refractory patients and thus do not address the issue of whether sPLA2-IIA remains upregulated in patients who have been subjected to hormone ablation therapy.

Referring the present case, Dr. Scott notes that the data in the patent application identify sPLA2-IIA as remaining upregulated in patients following hormone ablation therapy and, thus, link treatment with inhibitors directly to patients post hormone ablation therapy. Because, in these studies, the cancer cells have also failed to be removed by hormone ablation therapy, they have very likely already undergone progression to androgen independence. In addition, the declaration notes that the biochemical mechanisms by which progression to androgen independence occurs are highly heterogeneous, with at least five different pathways by which androgen independence can develop being recognised (Feldman and Feldman (2001); Exhibit 4 hereto). Thus *in vitro* progression to androgen independence of clonal cells in culture (as discussed in Graff) is not, according to Dr. Scott, necessarily predictive of progression to androgen independence *in vivo*. The present application shows that sPLA2-IIA levels remain elevated in prostate tissues posthormone ablation therapy (androgen withdrawal), thus establishing that sPLA2-IIA remains elevated in the clinical entity hormone refractory prostate cancer, rather than the laboratory entity of androgen independence.

In contrast to the cell culture studies in Graff, the declaration notes that the studies on tissue levels of sPLA2-hA in Graff relate to malignant progression if patients with benign prostate hyperplasia (BPH) (non-malignant cells) are compared relative to patients with low grade or high grade localised cancer (malignant cells). However, these tissue studies do <u>not</u> relate to progression to androgen independence since the androgen status of the patients is unknown. Rather, Dr. Scott notes that the studies on

tissue levels of sPLA2-IIA described by Graff relate to malignant progression in comparing patients with BPH relative to patients with primary cancer.

Finding (ii) by Graff is based on comparison of benign prostatic hyperplasia tissues (nonmalignant) with "low" grade (mean Gleason score 4.6) and "high" grade (mean Gleason score 7.0) primary tumours. Again, Dr. Scott observes that these studies relate to early stage prostate cancer.

Finding (iii) is based on the observation that a marker of cell proliferation (Ki67) is higher in prostate tissues that showed uniform sPLA2-IIA compared to prostate tissues that showed focal staining. The declaration observes that of the 19 tissues with uniform staining, 8/19 (42%) were from patients with benign prostate hypersplasia (BPH) (non-malignant) (Table I). Thus, the association with proliferation index does not in fact relate to malignant progression at all, since, according to the declaration, almost half of the tissues in the group studied are nonmalignant. The relationship between "uniform sPLA2-IIA staining" and proliferation index could equally apply to non-malignant tissues. It is clear to Dr. Scott that this analysis in Graff does not represent advanced prostate cancers, but a combination of benign prostatic hyperplasia (BPH) and cancer tissues.

Further, Dr. Scott notes that reference 29, cited in the last paragraph of Graff to back up the conclusion in (iii), discloses that "The transition of late-stage high-grade PiN cells into growing localised prostatic cancer cells involves no further increase in Kp [i.e. the rate of proliferation] but is due to a decrease in Kd" [i.e., the rate of cell death/apoptosis] (page 258, column 1, para 2., Denmeade *et al.,* 1996; Exhibit 3 hereto). Accordingly, the references quoted in the final paragraph of Graff in fact would

according to Dr. Scott suggest to the skilled person that targeting cell proliferation after malignancy progression would not be useful in treating late stage prostate cancer.

Finding (iv) does not show or suggest that inhibition of sPLA2-IIA-mediated proliferation will be of benefit, since as outlined by Dr. Scott earlier in the declaration, there are several ways tumors can be induced to regress that do not involve suppression of proliferation.

The declaration observes that in subsequent publications by Graff's research group, they have shown that elevation of sPLA2-IIA expression occurs even earlier than the primary cancer stage, before malignant progression (see Jiang *et al.,* 2002; Exhibit 5 hereto). The declaration notes that Exhibit 5 shows that sPLA2-IIA expression is elevated in low grade and high grade prostatic intraepithelial neoplasia (PiN), a condition which occurs in the early stages of prostate cancer (referring to Figure 1 in the declaration). Dr. Scott notes that this simply confirms what he believes a skilled person would understand from Graff that sPLA2-IIA expression is elevated during the early stage of prostate cancer and is involved in progression toward malignancy and androgen independence. According to Dr. Scott, there is nothing in Graff to suggest that sPLA2-IIA is elevated or would be a useful target in late stage cancer when progression to malignancy and androgen independence is already complete and other biochemical processes come into play.

Dr. Scott asserts his belief that the skilled person in the art would not have been motivated to treat late stage, prostate cancer in patients who have been subjected to androgen ablation therapy based on the findings of Graff. Dr. Scott observes that the present application is directed to treating a completely different class of patients (i.e.

terminal/late prostate cancer patients who have been subjected to androgen ablation therapy) than the class of patients to which Graff relates (i.e., prostate cancer patients with early stage prostate cancer who have not been subjected to androgen ablation therapy). As such, in the view of Dr. Scott, Graff would not have motivated the skilled person to use inhibitors of sPLA2-IIA to treat late stage prostate cancer in prostate cancer patients who have been subjected to androgen ablation therapy.

The declaration notes that Attiga shows that invasion of prostate cancer cells is inhibited by a PLA2 inhibitor, a general COX inhibitor and a selected COX-2 inhibitor, that Liu relates to a COX-2 inhibitor and that Kelavkar relates to a 1 5-lipoxygenase inhibitor. Dr. Scott concludes that a skilled person would not have found it obvious to take the findings of any of these references, which relate to completely different enzymes, alone or in combination with Graff or Church with a reasonable expectation of successfully arriving at a method for treating sPLA2-IIA-mediated proliferation of late stage prostate cancer in patients who have been subjected to androgen ablation therapy.

The declaration concludes by observing that the present application is directed towards inhibition of the ability of the sPLA2-HA polypeptide to catalyse the hydrolysis of membrane phospholipids at the sn-2 position to release fatty acids and lysophospholipids. Neither Graff nor any of the Attiga, Liu, Ketavkar or Church references, shows or suggests, in Dr. Scott's opinion, which activity of the enzyme must be inhibited, as presently claimed. Further, Dr. Scott observes that neither Graff nor any of the Attiga, Liu, Kelavkar or Church references, shows or suggests which form of the enzyme should be inhibited, as presently claimed.

Based on the above, it is clear that claimed subject matter of the present application would not have been obvious to a skilled person as of the filing date of the present application. Withdrawal of the obviousness rejections is respectfully requested.

Favorable action on this application is awaited.

Respectfully submitted,

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